anesthetics through the skin are as follows: (1) Drugs more readily penetrate to the subcutaneous receptor sites through damaged skin than through intact skin. Therefore, the effect of topical anesthetic products may be enhanced when they are applied to abraded, scratched, or burned skin. (2) Drugs penetrate hydrated skin and thin skin (for example, in the groin area) more readily than thick skin (such as on the palms of the hands). (3) Penetration may be affected by certain disease conditions such as eczema, which causes thinning of the skin; by product formulation; or by ionization of the active ingredient.

Because of these factors and because the Panel felt that there is no recognizable difference in effectiveness between anesthetics and analgesics, the Panel recommended that topical analgesics and anesthetics that depress cutaneous sensory receptors bear the same indication: "For the temporary relief of minor aches and pains of * * *". The agency believes that consumers would be misled if an external analgesic product were labeled as providing "complete temporary relief," "completely stops," or "completely blocks" minor aches and pains. The agency concurs with the Panel's recommended wording ("for the temporary relief of") and is proposing this wording in the tentative final monograph.

25. Two comments stated that the following language should be allowed in the labeling of external analgesic drug products, based on language that was not recommended by the Panel but was contained in its report: "for relief of pain in joints, muscles, tendons," "relieves pain without causing numbness," "completely blocks pain receptors," "relieves pain by reducing inflammation," "numbs and abolishes responses to painful stimuli," and "rheumatism."

The Panel allowed the claim "for the temporary relief of minor aches and pains of muscles and joints." The agency concurs with the Panel that the indications for OTC external analgesic drug products should emphasize that these products relieve only minor pain and have an action that is only temporary. The Panel did not review data on the use of external analgesic drug products for relief of pain in tendons, nor did the comment submit any data. Thus the agency is not proposing a claim for relief of pain in tendons until data are submitted to demonstrate the effectiveness of external analgesic drug products at these sites.

Claims regarding numbness or similar claims, such as completely blocking pain receptors or abolishing responses to painful stimuli, may be misleading to consumers because the manner in which external analgesic drug products are used determines whether they cause numbness or not. For example, the application of a product on abraded skin may cause numbness because of increased absorption that occurs, whereas application of the same product on intact skin may not cause numbness. (See comment 24 above.)

The agency believes that the term "reducing inflammation" should not be included as an indication—except when the term "inflammation" is used as a descriptive term related to the relief of itching associated with the nonserious conditions in the recommended indication for hydrocortisone and hydrocortisone acetate. (See comment 29 below for further discussion.) While the terms "arthritis" and "rheumatism" are used interchangeably by some consumers, "arthritis," the more accurate and precise term, is more readily understood by the majority of consumers. Substituting the term "rheumatism" probably would not increase consumers' understanding of the use of counterirritants and might cause confusion. In addition, the agency proposes to delete the terms "lumbago" and "neuralgia" from the Panel's recommended labeling in § 348.50(b)(1) because they are not readily understood by consumers. The revised indication in § 348.50(b)(1) for external analgesic products containing counterirritant active ingredients is as follows: "For the temporary relief of minor aches and pains of muscles and joints" [which may be followed by: "associated with" (select one or more of the following: "simple backache," "arthritis," "strains," "bruises," and "sprains."]]

26. Three comments disagreed with the Panel's placement of claims such as "relief of deep-seated pain," "deep strength," and "penetrating heat relief" in Category III. The comments claimed this classification was inconsistent with various statements made by the Panel about the mechanism of action of counterirritants (44 FR 69779), and the following statement regarding methyl salicylate: "methyl salicylate acts as a counterirritant for the temporary relief of deep-seated pain" (44 FR 69830). The comments maintained that relief of "deep-seated pain" is an established benefit of counterirritant ingredients, and that claims such as "deep strength," "penetrating heat relief," and "relief of deep-seated pain" should be acceptable claims along with claims such as "penetrating relief" that were found acceptable by the Panel.

One comment argued that the following labeling terms that the Panel placed in Category II are not misleading or meaningless to consumers: "fast," "swift," "sudden," "immediate," "prompt," "poignant," and "bright." The comment added that the Panel did not give any reason why the term "fast" was considered misleading. Another comment stated that studies submitted to the Panel show that certain external analgesic ingredients do act within minutes, and their action may be considered "fast" in layman's terms, pointing out that the Panel failed to describe what time period would be acceptable as "fast," i.e., what data it considered sufficient to support this claim.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

As with all OTC drug products, external analgesics are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which external analgesics achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast," "prompt," "swift," "sudden," and "immediate" would not signal any property that is important to the safe and effective use of these products, and these terms are outside the scope of the OTC drug review. For other classes of products in the OTC drug review, however, statements relating to time of action may properly fall within the list of terms covered by the monograph. Likewise, claims concerning nontherapeutic characteristics of drugs such as color, odor, or touch [e.g., "bright," "poignant," "pleasantly scented," or "greaseless"], as discussed

by the Panel at 44 FR 69784–69785, are not dealt with in OTC drug monographs. The agency emphasizes that even though these terms are outside the scope of the OTC drug review, they are subject to the prohibitions in section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Such terms will be evaluated by the agency in conjunction with normal enforement activities relating to that section of the act. Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

Claims concerning characteristics of therapeutic performance (e.g., "penetrating heat relief") will be dealt with only in cases where they imply the existence of a characteristic that would be therapeutically significant for the drug in question, if proved. The agency tentatively concludes that the statement "penetrating heat relief" does not describe therapeutically significant performance characteristics and will not be dealt with in this monograph. Accordingly, "penetrating heat relief" has been deleted from the section on Category III labeling (444 FR 69857). For the same reason, statements such as "penetrating relief," "warm comforting relief," and "penetrating cooling action," which were found reasonable and informative to consumers by the Panel (44 FR 69785), will not be dealt with in this tentative final monograph. The claim "penetrating pain relief," however, does describe a therapeutically significant performance characteristic by explaining the effect of counterirritants in language easily understood by consumers. However, the agency agrees with the Panel that this statement and similar ones should not be included as indications (44 FR 69785). Accordingly, the agency is proposing new § 348.50(b)(4) in this tentative final monograph under the heading "Other allowable statements," to include statements describing pain relief, as follows:

(4) *Other allowable statements.* In addition to the required information specified in this paragraph and in paragraphs (a), (b), (c), and (d) of this section, the labeling of the product may contain any of the following statements, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(i) For products containing any ingredient identified in § 348.12.

(*a*) (optional: "provides") "penetrating pain relief."

(*b*) (optional: "provides") "warming pain relief."

(*c*) (optional: "provides") "cool pain relief."

(ii) [Reserved]

The agency finds that the term "deep strength" is vague and conveys no useful information to consumers. A number of interpretations are possible. The term could refer to the extent of pentration of the drug, the potency or concentration of the drug, or the depth of action of the drug. The "depth" of action is dependent upon the absorption of the drug and not necessarily upon its concentration. Other interpretations are entirely possible. Because this term could be interpreted in various ways, the agency considers the term "deep strength" too confusing and vague and therefore does not propose to include it in this monograph. In addition, the agency has reviewed the references cited by the Panel at 44 FR 69830 (Refs. 1 through 5) in support of its statement that "methyl salicylate acts as a counterirritant for the temporary relief of deep-seated pain" and determined that these references do contain adequate data to establish that counterirritant active ingredients relieve pain distal to the site of application. Despite the Panel's statement, the agency concludes that claims for "relief of deep-seated pain" are not suitable for OTC counterirritants. Deep-seated pain may be caused by a serious condition not amenable to self-diagnosis and treatment. The claim is therefore not included in this monograph.

References

(1) Krantz, J. C., Jr., and C. J. Carr, "Pharmacological Principles of Medical Practice," 6th Ed., The Williams and Wilkins Co., Baltimore, p. 200, 1965.

(2) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 993, 1970.

(3) Crossland, J., "Lewis's Pharmacology," 4th Ed., E. and S. Livingstone, London, pp. 562–563, 1970.

(4) Fulton, G. P., E. M. Farber, and A. P. Moreci, "The Mechanism of Action of Rubefacients," *The Journal of Investigative Dermatology*, 33:317–325, 1959.

(5) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, p. 1036, 1971.

27. One comment disagreed with the recommendation that hydrocortisone be used for itchy genital and anal areas. The comment was concerned about the potential for absorption of hydrocortisone when used in the anogenital area and contended that the Panel's recommended warning to discontinue use and consult a physician if symptoms persist for more than 7 days will be ignored by many patients, and that frequent and chronic use of hydrocortisone in the genital areas may cause problems such as progression of an infection, dermal atrophy, and striae.

The Panel reached its conclusion that topical hydrocortisone is safe for OTC use in concentrations up to 0.5 percent for itchy genital and anal areas after a careful study of its use on all areas of the body, at a wide range of concentrations, and for prolonged periods of time (44 FR 69817 to 69822). In addition, the Panel found that dermal atrophy and striae are generally associated with the more potent fluorinated corticosteroids and have been reported only rarely for hydrocortisone, and then only after long-term or excessive use (44 FR 69817). Because these conditions can arise with long-term or excessive use, the agency is concerned about the adequacy of the Panel's recommended warning. Consumers may use hydrocortisone in the anogenital area for itching, which may be alleviated after a few days of treatment. If the hydrocortisone is then stopped, the itching may recur within a few days and the consumer may again use hydrocortisone. Consumers may go through several cycles of starting and stopping treatment with hydrocortisone, and the Panel's 7-day warning would be inadequate to warn against such overuse. The agency believes that the warning should emphasize to consumers the need to consult a doctor not only for conditions that do not respond to self-treatment, but also for those that recur after such treatment with hydrocortisone. For this reason, the agency is proposing to revise the Panel's recommended warning as follows: "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor").

The agency further believes that hydrocortisone products that bear the indication for external genital itching need to include a warning to inform women not to use the drug in the presence of vaginal discharge. A vaginal discharge may be a symptom of an infection, for which hydrocortisone is not effective and professional treatment is needed. Accordingly, the agency is

proposing the following warning in § 348.50(c)(7): "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor").

The Panel recommended in § 348.50 (c)(1)(i) that all OTC external analgesic drug products bear the warning "for external use only." The agency believes it is necessary to emphasize that OTC drug products containing hydrocortisone are intended only for external use in the genital and anal areas and that this information should be included in the indications for use for these products. The agency is therefore proposing to change the wording of the indication for hydrocortisone to read: for relief of "* * * external (select one or more of the following: 'genial,' 'feminine,' and 'anal' itching." The term "feminine itching" has been added as an optional labeling term because it is a term that is commonly used and understood by consumers.

As will be discussed in the preamble of the advance notice of proposed rulemaking for OTC vaginal drug products, which will be published in a future issue of the Federal Register, three OTC advisory review panels have made recommendations to FDA pertaining to the use of various OTC drugs in and around the vagina.

The Antimicrobial II Panel recommended that certain antifungal drugs currently available only by prescription be considered generally recognized as safe and effective for "treatment of external feminine itching associated with vaginal yeast (candidal) infection." However, the agency dissented on the Panel's recommendation because of its concern about consumer's self-treating itching associated with a vaginal infection (47 FR 12480). While the agency disagrees with the use of OTC drug products to treat vaginal infections, the agency tentatively believes that hydrocortisone can be safely and effectively used OTC to relieve external itching around the vagina. The agency recognizes that consumers cannot identify the underlying causes of such itching, but is aware that hydrocortisone will produce symptomatic relief. If relief is not obtained or the itching recurs, the consumer is advised to discontinue use of the drug and to consult a doctor. The agency will further discuss the OTC use of antifungal drug products for this use in the tentative final monograph for that class of drugs.

In light of the different recommendations from the three panels, previous agency actions, and the comments submitted in response to the advance notice of proposed rulemaking for OTC antifungal drug products, there appears to be uncertainty regarding the use of OTC drug products for treating the system of external itching around the vagina. The agency is particularly concerned about (1) the ability of a woman to recognize the nature or cause of the itching in order to determine which kind of drug product to select to treat it, e.g., an antipruritic or antifungal for the external areas, including the vulva, and (2) whether one week of self-medicating with an OTC drug product containing hydrocortisone may pose an unacceptable delay in seeking professional attention if the symptom(s) are due to gonorrhea, trichomonas, candida, or other organisms which will not be eradicated by topical therapy with OTC drug products containing hydrocortisone. The agency is tentatively agreeing with the Topical Analgesic Panel that hydrocortisone can be safety used OTC for relief of itching if accompanied by appropriate warnings but is inviting specific comment on this issue, and particularly invites comment from gynecologists, family practitioners, and other health professionals.

28. One comment requested that the Panel's recommended indication for antipruritic ingredients in § 348.50(b) (2) be expanded to allow the general claim "for the relief of itching." The comment argued that there is no scientific basis for limiting the claim to itching due only to minor burns, sunburn, minor cuts, abrasions, insect bites, and minor skin irritations. The comment concluded that the antipruritic properties of the ingredients included in § 348.10(b) provide relief no matter what stimulates the local itching sensation, and consumers should be informed accordingly.

The agency agrees with the comment that products containing antipruritic ingredients should be allowed to use the indication "For the temporary relief itching" without listing examples of causes of itching. Such labeling would be clearly recognizable and meaningful to a consumer who was experiencing itching without knowing the cause. The agency is therefore proposing that products containing antipruritic ingredients may be labeled for itching only or for itching associated with one or more causes. The agency is also proposing the same type of alternative labeling for hydrocortisone product. In addition, in order to improve clarity and to simplify OTC labeling, the agency is proposing to use the word "scrapes" instead of "abrasions" in the proposed indication for antipruritics in § 348.50(b)(2).

Based upon the above discussion, and the discussion in comment 27 above, the following indications are being proposed in the tentative final monograph as § 348.50(b) (2) and (3):

(2) *For products containing any external analgesic active ingredients identified in § 348.10 (a), (b), and (c).* "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritations.")]

(3) *For products containing any external analgesic active ingredients identified in § 348.10(d).* "For the temporary relief of itching associated with minor skin irritations and rashes" [which may be followed by: "due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry,") and/or ("and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.")]

29. Several comments requested that the term "inflammation" be added to the indications for OTC hydrocortisone drug products or that the term "anti-inflammatory" be used as the statement of identity for these products. The comments stated that it is medically inaccurate and incomplete to categorize hydrocortisone only as an antipruritic or external analgesic, because the relief of itching or pain is secondary to its anti-inflammatory action. The comments pointed out that the principal pharmacologic action of hydrocortisone has long been recognized as anti-inflammatory, and consumers should be informed of this activity to allow proper use of the ingredient.

In its review of hydrocortisone, the Panel acknowledged that numerous studies over a 20-year period have demonstrated the effectiveness of topical hydrocortisone preparations as antipruritic (anti-itch) and anti-inflammatory agents and that hydrocortisone preparations are frequently used as anti-inflammatory agents (44 FR 69813–69824). Nevertheless, the Panel recommended that hydrocortisone for OTC use bear labeling related only to its anti-itch activity and recommended an indication statement that specified use for nonserious conditions that the Panel believed consumers could appropriately self-medicate with hydrocortisone.

The statement of identity is intended to communicate to consumers the principal intended action of a drug in terms that are meaningful to the layman. The agency agrees with the Panel that

the principal intended OTC use of hydrocortisone drug products is to relieve itching. As discussed in comment 21 above, the agency is proposing "anti-itch" as the statement of identity for OTC hydrocortisone drug products. Although hydrocortisone does have an anti-inflammatory action, as the comment and the Panel acknowledged, the agency does not believe that the term "anti-inflammatory" should be included in the OTC statement of identity for products containing hydrocortisone. Inclusion of the term "anti-inflammatory" in the statement of identity may suggest to consumers that the product is intended for self-medicating serious conditions that should be treated by a doctor. The term "anti-inflammatory" may be used in the professional labeling of products containing hydrocortisone, as described in the class labeling guideline for topical corticosteroids (Ref. 1).

As mentioned in comment 28 above, the agency believes that the Panel's recommended indication needs to be revised to emphasize the OTC use of hydrocortisone preparations to relieve itching. The agency further believes that "inflammation" could be included as an optional descriptive term in the indication statement for hydrocortisone, so long as it is related to the relief of itching associated with the nonserious conditions included in the recommended indication. Therefore, the agency is proposing the following optional indication to be added as § 348.50(b)(3)(ii) of the tentative final monograph: "For the temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry,") (which may be followed by: "and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.") The agency believes that the above indication will inform consumers about the anti-inflammatory properties of hydrocortisone while limiting its OTC use to specific nonserious conditions and thus help to prevent misuse of hydorcortisone for inflammation associated with infection. Further, the agency believes that the warning proposed as § 348.50(c)(1)(iii), "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor,") provides additional protection to consumers against such misuse.

Reference

(1) Food and Drug Administration, "Topical Corticosteroids Class Labeling Guideline," Docket No. 81D-0274, Dockets Management Branch.

30. Two comments disagreed with the Panel's warning in § 348.50(c)(1)(iii), which states "If condition worsens, or if symptoms persist for more than 7 days, discontinue use of this product and consult a physician." The comments noted that existing FDA warnings for counterirritants and topical salicylates in 21 CFR 369.20 direct consumers to consult a physician if pain persists for more than 10 days. One comment stated that in light of the excellent safety record of external analgesic products and in the absence of any data to the contrary, the 10-day use limitation should be retained.

The agency agrees with the Panel that 7 days is sufficient time for the consumer to self-treat with external analgesic products before consulting a physician. If symptoms persist after 7 days, there may be an underlying disease or condition that requires a physician's diagnosis and treatment, and continuing to self-treat for more than 7 days may delay proper treatment. Furthermore, prolonged duration of use can increase the incidence of sensitivity and decrease effectiveness of external analgesic ingredients. As stated by the Panel at 44 FR 69781, these ingredients can have a direct irritating effect or may produce sensitization from prolonged or repeated contact with the skin. For example, the Panel pointed out that patients may develop tolerance to the effectiveness of tripelennamine hydrochloride and diphenhydramine hydrochloride or become sensitive to these drugs after more than 7 days of use (44 FR 69809 and 69839). When the final monograph for external analgesic drug products is published, those parts of § 369.20 covered by the monograph will be deleted.

31. One comment objected to the Panel's recommended warning in § 348.50(c)(2)(ii) for counterirritants, "Do not bandage." The comment argued that it is common practice in athletic training procedures to cover injuries after applying counterirritants either to protect clothing or to increase the stimulation of cutaneous receptors. The comment suggested that a warning such as "Bandage with caution" be substituted for the Panel's warning.

The agency agrees with the comment that it is desirable to protect clothing from stains by covering the application site, but believes that such covering should not be tightly applied. The agency is not aware of any evidence that the risk of adverse reactions to counterirritants increases when the application site is lightly covered, but is aware that under tight bandaging or occlusive dressing there is an increased risk of irritation, redness, or blistering. The Panel did not provide specific reasons for recommending the warning "Do not bandage" for counterirritants. However, counterirritants are, as the name itself implies, irritating, and occlusion by tight bandaging may increase their absorption through the skin. Therfore, it is proposed in this tentative final monograph that the Panel's recommended warning "Do not bandage" be revised to "Do not bandage tightly." The agency believes that this warning is more helpful to consumers because it provides more specific information and is therefore clearer than the warnings proposed by the comment.

32. One comment requested that the minimum age restriction for use of topical analgesic, anesthetic, and antipruritic ingredients be changed from 2 years to 6 months of age. The comment argued that because the Panel defined adult skin as "skin that is older than 6 months of age" (44 FR 69773), because the effect of occlusion under a diaper can be taken care of by use of an appropriate warning, and because a child under 2 years of age is well able to communicate pain by crying, these ingredients can be used safely on children over 6 months of age. In addition, the comment stated that these products are particularly useful for crawling infants who receive minor scratches, with related discomfort, that do not require a doctor's care.

The agency believes that external analgesic drug products should not be used on children under 2 years of age except as recommended by a physician. Although it is true that by 6 months of age a child's skin is similar to an adult's with regard to drug absorption, there are enough other differences betwen adults and children under 2 years of age to require different standards of practice in the use of drugs. Children 2 years of age above are just beginning to learn to communicate verbally in expressing their symptoms to a parent. At less than 2 years of age, the infant is more passive and less able to express and localize symptoms. Occlusion from a diaper, from lying on a waterproof mattress, or from body folds touching each other can enhance cutaneous absorption that can result in systemic effects in infants who do not have fully developed drug metabolism systems. Analgesic drugs can also be corrosive to infants' skin under occlusion. Parents could be warned against occlusion from a diape

but it would be difficult to warn them adequately against less obvious occlusion. Therefore, the agency agrees with the Panel that limiting use of these products to children 2 years of age or older except under the advice and supervision of a physician is necessary to provide an adequate margin of safety.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all the claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's categorization of ingredients except for camphorated metacresol and methapyrilene hydrochloride. (See paragraphs 11 and 15 under "Summary of the Agency's Changes in the Panel's Recommendations" below.) For the convenience of the reader, the following tables are included as summaries of the categorization of active ingredients recommended by the Panel and proposed by the agency.

Analgesic, anesthetic, and antipruritic active ingredients	Panel	Agency
Aspirin	I	I
Benzocaine	I	I
Benzyl alcohol	I	I
Butamben picrate	I	I
Camphor	I	I
Camphorated metacresol	III	III
Chloral hydrate	III	III
Chlorobutanol	III	III
Cyclomethycaine sulfate	III	III
Dibucaine	I	I
Dibucaine hydrochloride	I	I
Dimethisoquin hydrochloride	I	I
Diphenhydramine hydrochloride	I	I
Dyclonine hydrochloride	I	I
Eugenol	III	III
Glycol salicylate	III	III
Hexylresorcinol	III	III
Hydrocortisone [1]	I	I
Hydrocortisone acetate [1]	I	I
Juniper tar	I	I
Lidocaine	I	I
Lidocaine hydrochloride	I	I
Menthol	I	I
Methapyrilene hydrochloride	I	III
Phenol	I	I
Phenolate sodium	I	I
Pramoxine hydrochloride	I	I
Resorcinol	I	I
Salicylamide	III	III
Tetracaine	I	I
Tetracaine hydrochloride	I	I
Thymol	I	I
Trolamine salicylate [2]	III	III
Tripelennamine hydrochloride	I	I

[1] Hydrocortisone and hydrocortisone acetate are OTC external analgesics only for use as topical antipruritics.
[2] Identified by the Panel as triethanolamine salicylate.

Counterirritant ingredients	Panel	Agency
Allyl isothiocyanate	I	I
Strong ammonia solution [1]	I	I
Camphor	I	I
Capsaicin	I	I
Capsicum	I	I
Capsicum oleoresin	I	I
Chloral hydrate	I	I
Eucalyptus oil	I	I
Histamine dihydrochloride	III	III
Menthol	I	I
Methyl nicotinate	I	I
Methyl salicylate	I	I
Turpentine oil	I	I

[1] Identified by the Panel as ammonia water, stronger.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for external analgesic drug products (44 FR 69857). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. (See comment 14 above.)

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any external analgesic ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. The agency is proposing to include the combination of camphor and menthol in this tentative final monograph in new § 348.20(a)(6). (See comment 12 above.)

2. The agency proposes that 4.7 percent phenol be included in this tentative final monograph when it is combined with 10.8 percent camphor in accordance with § 348.20(a)(4). (See comment 13 above.)

3. The agency proposes changing the term "antipruritic," the Panel's recommended statement of identity for hydrocortisone products, to "antipruritic (anti-itch)," "anti-itch," antipruritic (anti-itch) *(insert dosage form, e.g., cream, lotion, or ointment),"* or "anti-itch *(insert dosage form, e.g., cream, lotion, or ointment)."* (See comment 21 above.)

4. Alternatives to the Panel's recommended statement of identity, "external analgesic," are being proposed in § 348.50(a)(1) as "external analgesic," "topical analgesic," or "pain relieving *(insert dosage form, e.g., cream, lotion, or ointment)*." (See comment 20 above.)

5. The agency proposes that terms such as "fast," "prompt," "swift," "sudden," and "immediate," which were classified by the Panel as Category II, and statements such as "penetrating heat relief" are outside the scope of the OTC drug review because they do not signal any property that is important to the safe and effective use of OTC external analgesic drug products. Claims such as "penetrating pain relief" do describe therapeutically significant performance characteristics of OTC counterirritant active ingredients and are included under a new section, § 348.50(b)(4), "Other allowable statements." (See comment 26 above.)

6. The 7-day warning recommended by the Panel for external analgesic drug products in § 348.50(c)(1)(iii) has been revised and is being proposed as follows in § 348.50(c)(1)(iii): "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" (select one of the following: "physician" or "doctor"). (See comment 27 above.)

7. The indications for analgesic, anesthetic, and antipruritic ingredients and for counterirritant ingredients are proposed in § 348.50(b) to allow the optional use of terms describing the conditions relieved by these ingredients and to include the general claim "for the relief of itching" for antipruritic ingredients. To improve consumer understanding, the agency proposes deletion of the term "dermatitis" from the indications for hydrocortisone drug products, while it proposes to add "feminine itching." The agency is also proposing an optional indication for hydrocortisone drug products. (See comments 22, 27, 28, and 29 above.)

8. The agency is proposing the following warning in § 348.50(c)(7) for hydrocortisone products that are labeled with the optional indication of external genital or feminine itching: "Do not use if you have a vaginal discharge. Consult a" (select one of the following: "physician" or "doctor"). (See comment 27 above.)

9. To provide clearer and more specific information to consumers, the agency proposes to revise the Panel's recommended warning for counterirritants in § 348.50(c)(2)(ii) to state: "Do not bandage tightly." (See comment 31 above.)

10. The following are agency-initiated changes in the Panel's recommended monograph based on the format and style of recently published monographs:

a. Section 348.10(a) has been redesignated § 348.12, and § 348.10(b) has been redesignated § 348.10.

b. The agency has redesignated proposed Subpart D of the monograph as Subpart C, placing the labeling sections under Subpart C.

c. The definitions sections has been revised to include only those definitions considered necessary for this tentative final monograph. The definitions under age for "infant, child, and adult" and the term "cutaneous sensory receptor" were deleted because they are not used in the labeling proposed in the tentative final monograph. The definitions for "topical analgesic" and "topical anesthetic" were combined under a new definition "analgesic, anesthetic" because the actions of a topical analgesic and a topical anesthetic are similar, and no distinction is made in the proposed indications section. (See comment 24 above.) A definition for camphorated metacresol has been added because the complex has been included in the monograph. (See comment 13 above.)

d. The subgroups of active ingredients listed in §§ 348.10 and 348.12 have been identified with headings that are in accordance with the Panel's recommendations.

e. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and other applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

f. The Panel's recommended warning in § 348.50(c)(1)(iv) has been deleted, and the following statement has been included under the directions in proposed § 348.50(d): "Children under 2 years of age: consult a" (select one of the following: "physician" or "doctor").

11. The agency has reclassified methapyrilene hydrochloride from Category I to Category II as an OTC external analgesic ingredient. A tentative final rule for nighttime sleep-aid., published in the Federal Register of June 13, 1978 (43 FR 25544), proposed to place methapyrilene in Category II because of preliminary studies implicating this drug as a carcinogen, or a carcinogen synergist with nitrates, in rats. However, at that time, the studies were too preliminary to support a definitive finding of carcinogenicity for methapyrilene itself that would necessitate its immediate removal from all products in the OTC drug market.

On May 1, 1979, the agency received an interim report from the National Cancer Institute (NCI) regarding carcinogenicity studies performed with methapyrilene at the Frederick Cancer Research Center. The results of these studies have been published by Lijinsky, Reuber, and Blackwell (Ref. 1). The NIC interim report stated that methapyrilene is a potent carcinogen in rats and must be considered a potential carcinogen in man. FDA reviewed this report and concurred with its conclusions. Industry agreed to a request from the agency to recall all methapyrilene-containing products from the market voluntarily. On June 15, 1979, FDA issued a recall letter to all manufacturers holding an approved new drug application (NDA) for products containing methapyrilene. This voluntary recall has virtually eliminated drug products containing methapyrilene from the marketplace. All human drugs containing methapyrilene for systemic or topical use are currently regarded as new drugs within the meaning of section 201(p) of the act (21 U.S.C. 321(p) and are subject to regulatory action under sections 502 and 505 of the act (21 U.S.C. 352 and 355).

References

(1) Lijinsky, W., M. D. Reuber, and B. N. Blackwell, "Liver Tumors Induced in Rats by Chronic Oral Administration of the Common Antihistamine Methapyrilene Hydrochloride," *Science*, 209:817–819, 1980.

12. Thymol has been deleted from recommended § 348.20(b)(1)(ii) as an ingredient for inclusion in combinations of external analgesic active ingredients. The Panel classified thymol as Category III. Thymol was inadvertently included in the Panel's recommended nonograph. The agency tentatively concurs with the Panel's Category III classification of thymol and is correcting this error in the monograph.

13. The agency is proposing to lower the upper concentration limit for phenol and phenolate sodium from 2 percent to 1.5 percent in external analgesic drug products. Monographs for other OTC drug products for external use limit the concentration of phenol to 1.5 percent. for example, the tentative final monograph for OTC Antimicrobial I drug products classified concentrations of phenol exceeding 1.5 percent as Category II for safety when used in antimicrobial soaps, patient preoperative skin preparations, health-care personnel handwashes, skin antiseptics, skin wound cleansers, skin wound products, and surgical hand scrubs. The agency stated in this document that the use of phenol in concentrations of 2 percent or more has caused serious hazards, including gangrene, mummification, and even coma (January 6, 1978; 43 FR 1227). The Panel on OTC Dentifrices and Dental Care Drug Products also placed phenol in concentrations above 1.5 percent in Category II as an oral mucosal analgesic (May 25, 1982; 47 FR 22739). The upper concentration limit of phenolate sodium, the sodium salt of phenol, is also being lowered to 1.5 percent so that it has the same limit as phenol.

An exception to this upper limit of 1.5 percent phenol has been made for phenol when combined with camphor. The agency has proposed that 4.7 percent phenol may be safely combined with 10.8 percent camphor. (See comment 13 above.)

14. The agency proposes that the warning recommended by the Panel in § 348.50(c)(5) for products containing phenol pertains also to products containing phenolate sodium and camphorated metacresol, and has amended the tentative final monograph accordingly in § 348.50(c)(5). The agency notes that the Panel used slightly different wording in the warnings it recommended in § 348.50(c)(3), (5), and (6) to convey the same message. To prevent consumer confusion, the agency has proposed the same wording, where applicable, in the warning statements in these sections. The Language in these warnings is taken from a similar warning that the agency proposed for topical antimicrobial drug products in the Federal Register of July 9, 1982 (47 FR 29986).

15. The agency is proposing to classify camphorated metacresol as Category I for safety and effectiveness and is including a definition of camphorated metacresol in § 348.3(b)—(See comment 13 above.)

16. For ease of understanding by consumers, the agency proposes to revise the warning recommended by the Panel in § 348.50(c)(3)(ii) as follows: "This product stains skin and clothing yellow."

The agency advises that those parts of §§ 310.201(a) (19) and (23), 369.20 and 369.21 applicable to external analgesic drug products will be revoked at the time that this monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 348

[Docket No. 78N-0301]

External Analgesic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) external analgesic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products and public comments on an advance notice or proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or request for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by April 11, 1983. New data by February 8, 1984. Comments on the new data by April 9, 1984. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Written comments on the agency's economic impact determination by June 8, 1983.

ADDRESS: Written comments, objections, or request for oral hearing to the Docket Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. New data and comments on new data should also be addressed to the Dockets Management Branch.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of December 4, 1979 (44 FR 69768) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC external analgesic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by March 6, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by April 3, 1980.

In a notice published in the Federal Register of September 26, 1980 (45 FR 63878), the agency advised that it had reopened the administrative record for OTC external analgesic drug products to allow for consideration of recommendations on camphor-containing drug products that had been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products after the date the administrative record previously had officially closed. The agency concluded that the Miscellaneous External Panel's recommendations should be available to the agency in developing a proposed regulation on external analgesic drug products in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the Federal Register on December 4, 1979 (44 FR 69768), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule), FDA states for the first time its position on the establishment of a monograph for OTC external analgesic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC external analgesic drug products.

In response to the advance notice of proposed rulemaking, 1 trade association, 10 drug manufacturers, 36 health professionals, and 4 consumers submitted comments. In response to the notice of reopening the administrative record to allow for consideration of recommendations on camphor-containing drug products, one trade association, six drug manufacturers, and one drug marketer submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish Part 348 (21 CFR 348) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC external analgesic drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established.

Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety and effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not

Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354).

Some external analgesic drug products may have to be reformulated to delete nonmonograph ingredients; however, there are a number of Category I ingredients available for reformulation. The agency believes that minimal testing of nonmonograph ingredients will be done because of the availability of other ingredients for reformulation. Manufacturers will have up to 12 months to revise their product labeling. In most cases, this will be done at the next printing so that minimal costs should be incurred. Thus, the impact of the proposed rule, if implemented, appears to be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC external analgesic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC external analgesic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on external analgesic drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of this proposal and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact, and the evidence supporting this finding, is contained in an environmental assessment (under 21 CFR 25.31, proposed in the Federal Register of December 11, 1979; 44 FR 71742), which may be seen in the Dockets Management Branch, Food and Drug Administration.

List of Subjects in 21 CFR Part 348

OTC drugs: External analgesics.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982)), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 348 to read as follows:

PART 348—EXTERNAL ANALGESIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

Subpart B—External Analgesic Active Ingredients

Subpart C—Labeling

Authority: Secs. 201 (p), 501, 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 348.1 Scope.

(a) An over-the-counter external analgesic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 348.3 Definitions.

As used in this part:

(a) *Analgesic, anesthetic.* A topically (externally) applied drug that relieves pain by depressing cutaneous sensory receptors.

(b) *Antipruritic.* A topically (externally) applied drug that relieves itching by depressing cutaneous sensory receptors.

(c) *Camphorated metacresol.* A complex consisting of camphor and metacresol combined in a ratio of 3 parts camphor to 1 part metacresol.

(d) *Counterirritant.* A topically (externally) applied drug that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles, joints, or viscera distal to the site of application by stimulating cutaneous sensory receptors.

(e) *External analgesic.* A topically (externally) applied drug that has a topical analgesic, anesthetic, or antipruritic effect by depressing cutaneous sensory receptors, or that has a topical counterirritant effect by stimulating cutaneous sensory receptors.

Subpart B—Active Ingredients

§ 348.10 Analgesic, anesthetic, and antipruritic active ingredients.

The active ingredients of the product consist of any of the following, within the established concentration for each ingredient:

(a) *Amine and "caine"-type local anesthetics.*

(1) Benzocaine 5 to 20 percent.

(2) Butamben picrate 1 percent.

(3) Dibucaine 0.25 to 1 percent.

(4) Dibucaine hydrochloride 0.25 to 1 percent.

(5) Dimethisoquin hydrochloride 0.3 to 0.5 percent.

(6) Dyclonine hydrochloride 0.5 to 1 percent.

(7) Lidocaine 0.5 to 4 percent.

(8) Lidocaine hydrochloride 0.5 to 4 percent.

(9) Pramoxine hydrochloride 0.5 to 1 percent.

(10) Tetracaine 1 to 2 percent.

(11) Tetracaine hydrochloride 1 to 2 percent.

(b) *Alcohols and ketones.*

(1) Benzyl alcohol 10 to 33 percent.

(2) Camphor 0.1 to 3 percent.

(3) Camphor 3 to 10.8 percent when combined with phenol in accordance with § 348.20(a)(4).

(4) Camphorated metacresol (camphor 3 to 10.8 percent and metacresol 1 to 3.6 percent).

(5) Juniper tar 1 to 5 percent.

(6) Menthol 0.1 to 4 percent.

(7) Phenol 0.5 to 1.5 percent.

(8) Phenol 4.7 percent when combined with camphor in accordance with § 348.20(a)(4).

(9) Phenolate sodium 0.5 to 1.5 percent.

(10) Resorcinol 0.5 to 3 percent.

(c) *Antihistamines.*

(1) Diphenhydramine hydrochloride 1 to 2 percent.

(2) Tripelennamine hydrochloride 0.5 to 2 percent.

(d) *Hydrocortisone preparations.*

(1) Hydrocortisone 0.25 to 0.5 percent.

(2) Hydrocortisone acetate 0.25 to 0.5 percent.

§ 348.12 Counterirritant active ingredients.

The active ingredients of the product consist of any of the following within the established concentration for each ingredient:

(a) *Irritants that producer redness*—(1) Allyl isothiocyanate 0.5 to 5 percent.

(2) Strong ammonia solution, diluted to contain 1 to 2.5 percent ammonia.

(3) Methyl salicylate 10 to 60 percent.

(4) Turpentine oil 6 to 50 percent.

(b) *Irritants that produce cooling sensation.*—(1) Camphor exceeding 3 percent to 11 percent.

(2) Menthol 1.25 to 16 percent.

(c) *Irritants that produce vasodilation.*—(1) Histamine dihydrochloride 0.025 to 0.10 percent.

(2) Methyl nicotinate 0.25 to 1 percent.

(d) *Irritants that do not produce redness.*—(1) Capsaicin 0.025 to 0.25 percent.

(2) Capsicum containing 0.025 to 0.25 percent capsaicin.

(3) Capsicum oleoresin containing 0.025 to 0.25 percent capsaicin.

§ 348.20 Permitted combinations of active ingredients.

(a) *Combinations of external analgesic active ingredients.*—(1) Any ingredient identified in § 348.10(a) may be combined with any ingredient identified in § 348.10(b).

(2) Any ingredient identified in § 348.10(b) may be combined with any ingredient in § 348.10(c).

(3) Any ingredient identified in § 348.10(b)(1), (5), (7), (9), and (10) may be combined with camphor and menthol identified in § 348.10(b)(2) and (6).

(4) Camphor and phenol indentified in § 348.10(b)(3) and (8) may be combined in a light mineral oil, USP vehicle.

(5) Any two, three, or four ingredients indentified in § 348.12 may be combined provided that the combination contains no more than one active ingredient from each group identified in § 348.12(a), (b), (c), and (d).

(6) Camphor identified in § 348.12(b)(1) may be combined with menthol identified in § 348.12(b)(2).

(7) Camphor and menthol identified in § 348.20(a)(6) may be combined with any one, two, or three ingredients identified in § 348.12 provided the combination contains no more than one ingredient from each group identified in § 348.12(a), (c), and (d).

(b) *Combinations of external analgesic active ingredients and other active ingredients.*—(1) Any ingredient identified in § 348.10(a), (b), or (c), or any combination identified in paragraph (a)(i), (2), or (3) of this section may be combined with any generally recognized safe and effective skin protectant active ingredient or skin protectant combination identified in Part 347 provided the product is labeled for the concurrent symptoms.

(2) Any ingredient identified in § 348.10(a), (b), or (c) or any combination identified in paragraph (a)(1), (2), or (3) of this section may be combined with any generally recognized safe and effective topical antimicrobial active ingredient or topical antimicrobial combination identified in Part 333, Subpart A, provided the product is labeled for the concurrent symptoms.

Subpart C—Labeling

§ 348.50 Labeling of external analgesic drug products

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as follows:

(1) *For products containing any ingredient identified in § 348.10(a), (b), and (c) and § 348.12.* The labeling identifies the product as an "external analgesic," "topical analgesic," or "pain relieving (*insert dosage form, e.g., cream, lotion, or ointment*)."

(2) *For products containing hydrocortisone or hydrocortisone acetate identified in § 348.10(d).* The labeling identifies the products as "antipruritic (anti-itch)," "anti-itch," "antipruritic (anti-itch) (insert dosage form, e.g., cream, lotion, or ointment)," or "anti-itch (insert dosage form, e.g., cream, lotion, or ointment)."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indication(s)" that is limited to the following:

(1) *For products containing any external analgesic active ingredients identified in §348.12.* "For the temporary relief of minor aches and pains of muscles and joints" [which may be followed by: "associated with" (select one or more of the following: "simple backache," "arthritis," "strains," "bruises," and "sprains."]]

(2) *For products containing any external analgesic active ingredients identified in §348.10(a), (b), and (c).* "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following: "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritations."))

(3) *For products containing any external analgesic active ingredients identified in § 348.10(d).* The labeling of the product contains one of the following indications: (i) "For the temporary relief of itching associated with minor skin irritations and rashes" [which may be followed by: "due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, or poison sumac," "soaps," "detergents," "cosmetics," "jewelry,") and/or ["and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching."]]

(ii) "For the temporary relief of itching associated with minor skin irritations, inflammation, and rashes due to" (select one or more of the following: "eczema," "insect bites," "poison ivy, poison oak, poison sumac," "soaps," "detergents," "cosmetics," and "jewelry") (which may be followed by: "and for external" (select one or more of the following: "genital," "feminine," and "anal") "itching.")

(4) *Other allowable statments.* In addition to the required information specified in this paragraph and in paragraphs (a), (b), (c), and (d) of this section, the labeling of the product may contain any of the following statements as appropriate for the product's formulation, provided such statements are neither placed in direct conjuction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(i) *For products containing any ingredient identified in § 348.12.*

(*a*) (optional: "provides") "penetrating pain relief."

(*b*) (optional: "provides") "warming pain relief."

(*c*) (optional: "provides") "cooling pain relief."

(ii) [Reserved]

(c) *Warnings.* The labeling of the product contains the following statements under the heading "Warnings."

(1) *For products containing any external analgesic active ingredient identified in §§ 348.10 and 348.12.* (i) "For external use only."

(ii) "Avoid contact with the eyes."

(iii) "If condition worsens, or if symptoms persist for more than 7 days or clear up and occur again within a few days, discontinue use of this product and consult a" [select one of the following: "physician" or "doctor"].

(2) *For products containing any external analgesic active ingredient identified in §348.12.* (i) "Do not apply to wounds or damaged skin."

(ii) "Do not bandage tightly."

(3) *For products containing butamben picrate identified in §348.10(a)(2).* (i) "Do not apply over large areas of the body."

(ii) "This product stains skin and clothing yellow."

(4) *For products containing any external analgesic active ingredient identified in §348.10(a)(3), (4), (7), (8), (10), and (11).* "Do not use in large quantities, particularly over raw surfaces or blistered areas."

(5) *For products containing camphorated metacresol identified in §348.10(b)(4), phenol identified in §348.10(b)(7) and (8), and phenolate sodium identified in §348.10(b)(9).* "Do not apply over large areas of the body or bandage."

(6) *For products containing resorcinol identified in §348.10(b)(10).* "Do not apply over large areas of the body."

(7) *For products containing hydrocortisone preparations identified in §348.10(d) (1) and (2) that are labeled with the indications "* * * for external genital itching," or "* * * for external feminine itching."* "Do not use if you have a vaginal discharge. Consult a" select one of the following: "physician" or "doctor").

(d) *Directions.* The labeling of the product contains the following statement under the heading "Directions": *Adults and children 2 years of age and older:* Apply to affected area not more than 3 to 4 times daily. Children under 2 years of age: consult a (select one of the following: physician or doctor).

Interested persons may, on or before April 11, 1983 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before June 8, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before February 8, 1984 may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before April 9, 1984. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on April 9, 1984. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: January 19, 1983.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Richard S. Schweiker,

Secretary of Health and Human Services.

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